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WHAT CAN RESEARCH ON SCHIZOPHRENIA TELL US ABOUT THE COGNITIVE NEUROSCIENCE OF WORKING MEMORY?

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Abstract—Work with individuals with lesions to specific brain regions has long been used to test or even generate theories regarding the neural systems that support specific cognitive processes. Work with individuals who have neuropsychiatric disorders that also involve neurobiological disturbances may be able to play a similar role in theory testing and building. For example, schizophrenia is a psychiatric disorder thought to involve a range of neurobiological disturbances. Further, individuals with schizophrenia are known to suffer from deficits in working memory, meaning that examining the work on the neurobiology of working memory deficits in schizophrenia may help to further our understanding of the cognitive neuroscience of working memory. This article discusses the pros and cons of extrapolating from work in schizophrenia to models of healthy working memory function, and reviews the literature on working memory function in schizophrenia in relationship to existing human and non-human primate models of the cognitive neuroscience of working memory.

Key words: working memory, schizophrenia, prefrontal cortex, parietal cortex.

There is a long history of using work with patients who have lesions to specific brain regions to test, validate, or even generate theories regarding the cognitive processes supported by particular neural systems. A famous example is the case of H.M., an individual who had a bilateral resection of the hippocampus and surrounding medial temporal areas (Scoville and Milner, 1957). Following this operation, H.M. demonstrated profound deficits in the ability to learn and/or retrieve new episodic and semantic memories, despite relatively intact cognitive functioning in other domains (Corkin, 1984; Scoville and Milner, 1957; Squire, 1987), helping to inspire decades of work on the role of the medial temporal cortex in episodic memory function. However, one challenge of working with such lesion patients is that they are relatively rare, and it is difficult to generate large samples of such individuals. Individuals with neuropsychiatric disorders are, unfortunately, much more common than individuals with focal brain lesions. Many theories of neuropsychiatric disorders such as schizophrenia suggest that these diseases are caused at least in part by disturbances in specific neural systems. As such, one can also use work with neuropsychiatric populations to potentially test and/or generate theories about brain–behavioral relationships. For example, a large body of work has demonstrated that individuals with schizophrenia have deficits in working memory (Goldman-Rakic, 1991; Park and Holzman, 1992), suggesting that studies of individuals with schizophrenia may shed light on the neural systems that support working memory. The goal of the current article is to discuss the pros and cons of doing so, and to provide examples of how research on schizophrenia can help to inform our understanding of the cognitive neuroscience of schizophrenia.

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Abbreviations: DIPPC, dorsal inferior PPC; DLPFC, dorsolateral regions of prefrontal cortex; FEF, frontal eye field; R PPC, right posterior parietal region; SEF, supplementary eye field; TMS, transcranial magnetic stimulation; VIPPC, ventral inferior posterior parietal cortex; VLPFC, ventral lateral prefrontal cortex.

Pros and cons

Before reviewing the research on schizophrenia that is relevant to understanding the cognitive neuroscience of working memory, it is important to discuss some of the pros and cons of attempting to use work on neuropsychiatric populations to inform theories of normative human brain function. In healthy humans, the most commonly used techniques for studying the neural bases of cognition are functional imaging methods such as evoked response potentials (ERPs), positron emission tomography (PET), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). While these techniques have contributed enormously to work on human cognitive neuroscience, they are at heart correlational techniques that can tell us whether a brain region is activated by a particular cognitive probe, but cannot tell us whether the brain region is necessary for that process. Recent work using transcranial magnetic stimulation (TMS), a technique that involves temporarily disrupting activity in a brain region, can potentially provide greater information about what neural systems are necessary for specific cognitive processes. However, work with TMS is still relatively rare, and is most useful for regions close to the surface, as it is difficult to apply to deeper brain structures. As such, research with individuals who have impairments in specific brain regions or systems can provide stronger evidence for the necessity of certain brain regions for specific cognitive processes. Thus, a clear "pro" of studying individuals with schizophrenia, a disorder thought to involve deficits in brain regions such as prefrontal cortex and medial temporal cortex function, is that this work be able to provide information about the degree to which intact function in these brain regions is necessary for successfully working memory performance.

It is also important, however, to acknowledge the very serious limitations involved in using work with schizophre-

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nia or other neuropsychiatry disorders to inform theories of normal brain function. First, individuals with neuropsychiatric disorders often do not have clear and identifiable lesions in a specific brain system. For example, individuals with schizophrenia do not have clear lesions in the prefrontal cortex that one can clearly and easily identify on a magnetic resonance scan. Instead, the nature of the neurobiological disturbances in schizophrenia are much more subtle, involving relatively small changes to brain volume or shape (Csernansky et al., 1983), neuronal cytoarchitecture (Selemon et al., 2003), or even neurochemical function (Grace, 1991). Second, to make matters even more complicated, individuals with schizophrenia or other neuropsychiatric disorders rarely have a single type of neurobiological impairment. For example, work on schizophrenia suggests impairments in a range of brain regions, including prefrontal cortex, medial temporal cortex, the thalamus, and the basal ganglia. Third, individuals with neuropsychiatric disorders often have a host of complicating factors that may contribute to neurobiological deficits that are not a core part of the disorder. For example, many individuals with disorders such as schizophrenia have co-morbid substance abuse or dependence problems that may themselves alter brain function. Fourth, many individuals with neuropsychiatric disorders are taking medication that may themselves alter cognition and/or brain function. For example, individuals with schizophrenia are usually taking antipsychotic medications that involve the dopamine system, as well as other neurotransmitter systems. The dopamine system clearly plays a critical role in working memory (Goldman-Rakic, 1995), and it possible that antipsychotic mediations may have a complicating influence on working memory function in schizophrenia.

There are, of course, approaches to dealing with some of the limitations inherent in studying neuropsychiatric disorders. For example, one can study populations of individuals who are currently (or preferably never) medicated. Such an approach would allow one to avoid complications associated with the potential influences of medications on cognition. Unfortunately, it is very difficult to conduct such work with unmedicated populations, both for ethical and practical reasons. In addition, if one finds very clear differential deficits or double dissociations in cognition or brain function among individuals with disorders such as schizophrenia, then this work may be able to more clearly inform our understanding of the cognitive neuroscience of cognition, despite the multifactorial nature of the neural basis of schizophrenia. In summary, the strength or clarity of interpretations that one can make regarding brain–behavior relationships in neuropsychiatric disorders needs to be modulated by the caveats associated with the limitations described above.

Cognitive neuroscience theories of working memory

Before discussing the evidence regarding the nature of WM deficits in schizophrenia, it is useful to briefly outline the major cognitive and neurobiological theories of WM. WM is typically defined as the ability to maintain and manipulate information over short periods of time. It is widely agreed that WM involves several different component processes. As described in detail in another contribution to this series, Baddeley's (1986) influential theory of WM distinguishes among four major components; 1) a short-term storage buffer for visual information that is often referred to as the visuo-spatial scratchpad; 2) a short-term storage buffer for verbal information referred to as the phonological loop; 3) a central executive component that guides the manipulation and transformation of information held within the storage buffers; and 4) the more recently described episodic buffer (Baddeley, 2000). Each of these major component processes of WM can also be further subdivided into processes, some of which have been associated with the function of specific brain systems. For example, the phonological loop is thought to involve articulatory rehearsal of phonologically based representations. A number of studies suggest that articulatory rehearsal is particularly dependent on regions of left ventrolateral prefrontal cortex (VLPFC), including Brodmann's areas 44 and 45. Functional imaging studies examining rehearsal show activation of this region (Chein and Fiez, 2001; Fiez et al., 1996), and lesions to this region impair rehearsal but not the ability to use phonological representation (Vallar et al., 1997). In contrast, the processing or storage of phonological representation is thought to be dependent on regions of left posterior parietal cortex, again based on data both from lesions studies and imaging studies in healthy humans (Fiez, 1997; Fiez et al., 1996; Jonides et al., 1998a; Ravizza et al., 2004; Vallar et al., 1997).

The specific component processes of the visual–spatial scratchpad are not as clear as those involved in the phonological loop. One hypothesis regarding how humans maintain spatial information is that we use covert shifts of attention to the spatial locations to be remembered, a process that has been referred to as attention-based rehearsal (Awh and Jonides, 2001; Awh et al., 1998). These covert shifts of attention are thought to depend, at least in part, on the same neural systems that support spatial attention processing, such as right posterior parietal cortex (Postle et al., 2004). Consistent with this hypothesis, imaging studies of spatial WM consistently demonstrate activation of right posterior parietal regions (R PPC) (Postle et al., 2004), and lesions to R PPC lead to selective deficits in spatial WM (Pisella et al., 2004). In addition to RPPC, studies of spatial WM also consistently activate regions such as the frontal eye fields (FEF) and the supplementary eye fields (SEF). Curtis et al. (2004) have recently argued that information about the spatial location of cue information is represented in PPC, but that information about the director of visual saccades is processed and/or maintained in FEF/SEF regions.

In many ways, the central executive component of WM is the least well-specified component in Baddeley's model, a problem clearly acknowledged by Baddeley (1986) and others. There are a number of different processes that are often referred to as being part of the central executive, including those involved in the manipulation of information being stored in the domain specific buffers, protection from interference due to competing information or decay across

time, temporal coding or sequencing, updating of the contents of WM, etc. At the most simplistic level, many of the processes associated with the central executive have been assumed to be supported by the dorsolateral regions of prefrontal cortex (DLPFC), typically Brodmann's areas 46 and 9 bilaterally. A great deal of empirical data, from both lesion studies and functional imaging studies in healthy humans to support the idea that DLPFC is indeed critical for many processes ascribed to the central executive (Smith and Jonides, 1999). However, regions other than DLPFC are also important for the processes ascribed to the central executive and we should not equate DLPFC and executive function. As one example, Jonides and colleagues (D'Esposito et al., 1999c; Jonides et al., 1998b) have shown that a region of left VLPFC is involved in the resolution of proactive interference, a process that many have ascribed to the central executive.

Other researchers have parsed the processes involved in WM by distinguishing between maintenance and manipulation (Owen, 1997; Owen et al., 1999; Petrides, 1995). In many ways, this distinction maps on to the division between buffer systems (maintenance) and the central executive (manipulation). A number of functional neuroimaging studies have suggested that DLPFC and VLPFC are differentially involved in maintenance versus manipulation components of WM. These studies suggest that VLPFC regions are engaged by both maintenance and manipulation processes (with the explanation that manipulation tasks almost invariably require maintenance of some type), while DLPFC regions are engaged primarily by manipulation processes (Curtis et al., 2000; D'Esposito et al., 1999b; Veltman et al., 2003) or by higher maintenance loads that may require chunking or reorganizing of the material to be maintained in WM.

A great deal of work in the cognitive neuroscience of WM has also focused on understanding the contributions of specific neurotransmitter systems. It is beyond the scope of this paper to review the literature on the role of these systems, as this body of work is now quite large. However, the dopamine system has likely received the most attention in this domain, driven in large part by the breakthrough work of Goldman-Rakic et al. (2000). These researchers demonstrated that WM function is impaired in non-human primates following 6-hydroxy-dopamine lesions in prefrontal cortex (Brozoski et al., 1979), or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic, 1994). Further, low dose dopamine agonists can improve WM in monkeys (Williams and Goldman-Rakic, 1995), especially in those with impaired performance associated with factors such as advanced age (Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000). Dopamine agents can also modulate WM function in humans, although the results in this domain vary as a function of facts such as the nature of the task, the ability level of the participants, and even their genetic makeup (for a review, see Barch, 2004). A number of researchers have postulated specific computational roles for dopamine in WM. For example, Cohen and Servan-Schreiber (1992) have suggested that dopamine serves to modulate the signal to noise ratio and to enhance the fidelity of representations in WM. More recently, Braver and Cohen (2001) have suggested that dopamine may serve as a cue for updating information in WM, and that phasic dopamine signals help to gate or regulate what information is loaded into WM, a process that can help to protect from interference due to distracting information.

Working memory function in schizophrenia

The overview of current models of WM described above can provide an organizing framework for examining the nature of WM deficits in individuals with schizophrenia. As described above, models of WM distinguish between processes involved primarily in the maintenance of information (e.g. the buffer systems) and those involved in central executive or manipulation processes. If one could demonstrate that individuals with schizophrenia have deficits in one aspect of WM (e.g. central executive or manipulation) and not another aspect (e.g. maintenance), the presence of such a dissociation would provide support for these being critical distinctions in normal WM function.

Phonological loop in schizophrenia

As described above, one of the key components of the maintenance of information in WM is thought to be the phonological loop. One can ask questions about whether the phonological loop is intact in schizophrenia either by examining performance on tasks thought to depend upon the phonological loop, or by examining the function of brain regions thought to support the phonological loop. Though no cognitive task measures a single process, some WM tasks are more dependent on the phonological loop than others. For example, serial recall tasks with relatively low numbers of items (such as digit span forward, Sternberg or Brown-Petersen paradigms) and no interference are considered by some to be prototypical phonological loop tasks. According to at least some researchers, such tasks require both intact articulatory rehearsal and intact phonological storage/representations to perform successfully, but do not necessarily require central executive processes. A number of studies have shown that individuals with schizophrenia demonstrate relatively intact performance on digit span forward tasks, particularly when the number of items is at or below WM span (7 ± 2) (Clare et al., 1993; Cohen et al., 1999; Fitzgerald et al., 2004; Park and Holzman, 1992; Rushe et al., 1998; Salame et al., 1998) and when there is no verbal interference (Fleming et al., 1995; Oltmanns and Neale, 1975). Other work has shown that individuals with schizophrenia do not show disproportionate impairment for recall of lists with phonologically similar versus dissimilar items, suggesting an intact ability to represent phonological information (Elvevag et al., 2002). Further, studies suggest intact serial position curves among individuals with schizophrenia (Wexler et al., 2002), which is indicative of intact articulatory rehearsal mechanisms. However, work by Wexler and Stevens (Stevens et al., 1998; Wexler et al., 1998) has suggested that at least a subset of patients may have deficits in a verbal serial recall task that specifically probes for position information, more

so than on tone serial recall task. Further, a recent meta-analysis of the performance of individuals with schizophrenia did find significant impairment on digit span forward, though with a relatively small effect size compared with performance in other memory domains (Aleman et al., 1999).

One can also ask whether there is any evidence that individuals with schizophrenia are differentially impaired on verbal as compared with non-verbal WM tasks as another way to address the integrity of the phonological loop in schizophrenia. Many of the studies that have directly compared verbal WM to non-verbal WM in individuals with schizophrenia have found equal deficits across domains (Barch et al., 2002; Franke et al., 1999; Walter et al., 2003) or sometime worse non-verbal than verbal WM (Salame et al., 1998). Further, a recent meta-analysis of WM function in schizophrenia concluded that there was little evidence for any domain specific WM deficit in schizophrenia (Lee and Park, in press).

A third approach to determining whether the phonological loop is intact in schizophrenia is to determine whether individuals with schizophrenia show functional abnormalities in brain regions thought to be critical for phonological loop function. As described above, such regions include left VLPFC (BA 45 and 44) as well as left PPC. Examination of the WM-related functional activation literature suggests that the vast majority of studies report intact activation of VLPFC regions during WM performance in individuals with schizophrenia. For example, a recent review of studies using the N-back test of WM found that only three of 16 studies found any evidence for impaired VLPFC activity in schizophrenia (Barch, 2005). Studies using other types of WM tasks have also reported intact activation of VLPFC regions in individuals with schizophrenia (Barch et al., 2001; MacDonald and Carter, 2003; Manoach et al., 2000). Interestingly, these findings of intact activation in left VLPFC during WM tasks with verbal materials are consistent with the findings of a recent postmortem study which did not find cell density changes in Brodmann's area 44 (Selemon et al., 2003), though such changes are found in Brodmann's area 9, as discussed in more detail below.

Although the majority of functional imaging studies using WM tasks in schizophrenia report intact activation in VLPFC, a number of these same studies report abnormal activation in PPC, either in terms of the degree of activation or connectivity with other brain regions (Barch et al., 2002; Kim et al., 2003; Menon et al., 2001; Meyer-Lindenberg et al., 2001; Quintana et al., 2003; Schlosser et al., 2003a). Further, a number of imaging studies using the N-back WM task in schizophrenia have found abnormal PPC activation (Barch, 2005). Importantly, however, recent work by Fiez and colleagues has demonstrated that there are multiple regions of posterior parietal cortex active during WM tasks (Ravizza et al., 2004). One of these regions is sensitive to the type of information (verbal versus non-verbal) being maintained in WM and potentially corresponds to a left PPC region that supports phonological storage. The other PPC area was bilateral and sensitive to load irrespective of material type, and may play a role in the maintenance or updating of information in WM across stimulus domains. The region sensitive to material type was more ventral than the region sensitive to load, and Fiez and colleagues have referred to these different PPC regions as ventral inferior PPC (VIPPC) and dorsal inferior PPC (DIPPC) respectively. As such, it is important to determine which of these regions of PPC tends to show altered activation in individuals with schizophrenia, as evidence of impaired VIPPC function in schizophrenia may point to a disturbance in phonological store or processing that could contribute to maintenance disturbances in WM. However, recent work specifically focused on examining the integrity of VIPPC versus DIPPC activation in schizophrenia during WM found intact VIPPC activity in schizophrenia (Barch and Csernanksy, submitted for publication). Thus, the work using functional imaging to study brain function in schizophrenia suggests relatively intact function of the brain regions thought to support the phonological loop, including VLPFC and VIPPC. In sum, the work on schizophrenia suggests that the function of the phonological loop is relatively intact in this disorder. As will be discussed in further detail below, this contrasts with the wealth of data indicating deficits in central executive function. As such, the dissociation between deficits in central executive function, but not phonological loop function (or at least less severe in the phonological loop) provides evidence for the proposal that this represent distinct components of working memory that may have different neural substrates.

Visual–spatial scratchpad in schizophrenia

The critical behavioral and neural biological markers of scratchpad functions in healthy humans are much less clear than the markers of phonological loop function. Thus, it is more challenging to determine whether there may be selective disturbances in visual–spatial scratchpad function in schizophrenia. Among individuals with schizophrenia, there is certainly a large body of evidence for impairments on visual–spatial WM tasks, starting with the seminal work of Park and Holzman (1992). Further, there is consistent evidence for impairments on classic measure of the visual–spatial scratchpad, such as memory-guided saccade performance (McDowell et al., 2001; McDowell and Clementz, 1996; Muller et al., 1999; Snitz et al., 1999). However, as discussed above, there is little evidence for a selective deficit in spatial WM as compared with non-spatial WM in individuals with schizophrenia (Lee and Park, in press; Walter et al., 2003). Surprisingly, there are relatively few functional neuroimaging studies in schizophrenia that have used visual–spatial WM tasks that could not be accomplished by verbal recoding (small numbers of spatial locations are typically verbally labeled by participants, turning the task into a verbal WM task). Thus, more studies specifically designed to selectively assess visual–spatial scratchpad functions are needed to help understand the integrity of these processes and the brain regions that support them in schizophrenia.

In summary, much of the work on verbal and/or visual–spatial buffer systems in schizophrenia does not present

clear evidence for impairments in the maintenance of information in WM. Though there is some evidence for deficits on digit span forward type tasks, the effect size for these impairments is relatively small compared with impairments in other memory domains. Further, many other markers of the function of the phonological loop appear to be intact in schizophrenia, such as evidence for phonological similarity effects in WM. The work on functional brain imaging also suggests relatively little evidence for clear impairments in brain regions thought to be critical for phonological loop function, such as VLPFC or VIPPC. Again, the relatively intact function of the buffer systems in schizophrenia, combined with the work indicating deficits in central executive function reviewed below, provides validation for the distinctions made between buffer systems and central executive functions.

Central executive function in schizophrenia

In contrast to the mixed evidence for deficits in the verbal or visual–spatial buffer systems in schizophrenia, there is very consistent evidence that individuals with schizophrenia have difficulty with processes attributed to the central executive component of WM. As noted above, many studies suggest that individuals with schizophrenia have deficits on WM tasks with all different material types, with relatively little evidence for selective deficits with one material type over another (Barch et al., 2002; Coleman et al., 2002; Gooding and Tallent, 2004; Kim et al., 2004; Tek et al., 2002). Such a pattern is consistent with a deficit in central executive function (important for all material types) rather than a domain specific buffer system. In addition, individuals with schizophrenia consistently show deficits on tasks designed to measure a range of functions ascribed to the central executive, including manipulation (Gold et al., 1997; Kim et al., 2004), interference control and/or dual-task coordination (Fleming et al., 1995; Goldberg et al., 1998), and information updating and temporal indexing (Ganzevles and Haenen, 1995; Goldberg et al., 2003; Perlstein et al., 2003). Of note however, the majority of these studies have not dealt with the issue of differential deficits and have used measures of central executive function that likely have higher discriminating power than the "control" measures. A recent exception to this is work that compared maintenance only measures of WM to maintenance plus manipulation measures in individuals with schizophrenia and found a differential deficit on the manipulation measures (Kim et al., 2004; Kimberg et al., 1997; Kimberg and Farah, unpublished observations). Such results mirror early work by Oltmanns and Neale (1975) demonstrating a differential deficit on a digit span task that required protection from interference (a putative central executive function) as compared with a version that did not include such distraction. These authors demonstrated that the maintenance only measures have similar discriminating power to the maintenance plus manipulation measures, providing evidence against a generalized deficit interpretation of the results.

As described above, the basic cognitive neuroscience literature has linked many of the central executive components of WM to the function of DLPFC. Consistent with this hypothesis, a large number of functional neuroimaging using tasks that engage central executive components of WM have found disturbed DLPFC activation among individuals with schizophrenia. These studies have included tasks such as the Wisconsin Card Sorting Task (Berman et al., 1986, 1988; Weinberger et al., 1986, 1988), mental arithmetic (Hugdahl et al., 2004), self-ordered pointing, and various versions of the N-back task (Callicott et al., 2000; Carter et al., 1998). In most of the earlier studies using the Wisconsin Card Sorting task (Davidson and Neale, 1974), as well as in a number of the more recent studies using tasks such as the N-back and mental arithmetic, the modal finding has been of decreased activation in DLPFC in schizophrenia (Barch et al., 2002; Callicott et al., 1996, 2003; Carter et al., 1998; Fletcher et al., 1998; Honey et al., 2003; Hugdahl et al., 2004; Jansma et al., 2004; Mendrek et al., 2004, 2005; Menon, 1993; Meyer-Lindenberg et al., 2002, 2005; Perlstein et al., 2001; Quintana et al., 2003; Wykes et al., 2002). However, in several recent studies using the N-back and other WM tasks, researchers have reported either no changes in DLPFC (Honey et al., 2002; Kindermann et al., 2004; Manoach et al., 1999; Stevens et al., 1998; Walter et al., 2003), or increased activation in DLPFC among individuals with schizophrenia (Callicott et al., 2000, 2003; Jansma et al., 2004; Manoach et al., 2000; Quintana et al., 2003; Sabri et al., 2003) that sometimes co-occurred with decreased DLPFC activation in different regions.

One hypothesis put forth to explain these apparently contradictory findings regarding the direction of activation changes in DLPFC among individuals with schizophrenia is the idea that the memory load-DLPFC response curve may be different for individuals with schizophrenia as compared with healthy controls. A typical finding in healthy individuals is that DLPFC activity increases as memory load increases, until WM capacity is exceeded, at which point DLPFC activity decreases (Braver et al., 1997; Callicott et al., 1999; Cohen et al., 1997). Callicott and colleagues (2000, 2003) have suggested that the relationship between memory load and DLPFC activity may be different in individuals with schizophrenia, in one of two ways: 1) same load-activity curve, but a lower WM capacity, leading to a drop-off in DLPFC activity at lower memory loads as compared with controls; or 2) different load-response curve, such that patients show greater DLPFC activity than controls as lower memory loads (referred to as inefficient DLPFC activity), but less DLPFC activity than controls as higher memory loads. A recent review (Barch, 2005) and a recent meta analysis (Glahn et al., 2005) of N-back studies of WM in schizophrenia both suggested that the majority of the research results supports the first hypothesis, with few studies reporting evidence for hyper-DLPFC activation, even when groups are matched on behavioral performance, or high performing patients are compared with controls. Further, the review suggested that the regions of DLPFC showing hyperactivation in some WM studies may be distinct from the DLPFC regions that show hypoactivation, tending to be either more anterior

(particularly on the right) or more inferior (particularly on the left) (Barch, 2005). Such findings raise the possibility that activity of some of these regions may reflect compensatory strategies that are engaged when impairments in the DLPFC regions most commonly activated by central executive components of WM (i.e. BA 46/9) are not able to function properly. Further research that directly compares different WM paradigms that may elicit the use of different types of strategies, or research using paradigms specifically designed to manipulate or constrain the type of processes that can be used to accomplish the task, may help to parameterize the conditions under which individuals with schizophrenia show hyper- or hypo-DLPFC activation.

Although DLPFC is the region most commonly associated with central executive functions in humans, there is a large body of evidence to suggest that regions of parietal cortex are also important for central executive processing (Corbetta et al., 2002; Marshuetz et al., 2000; Peers et al., 2005; Ravizza et al., 2004; Sohn et al., 2000). As described above, there are several different regions of PPC activated in WM tasks, and Fiez and colleagues have suggested that the DIPPC regions are those most likely to plan a role in central executive processing (Ravizza et al., 2004). In a recent study designed to examine the integrity of VIPPC versus DIPPC in schizophrenia, we found clear evidence for impaired DIPPC function during both verbal and nonverbal WM performance, in the same individuals who demonstrated intact VIPPC function. Findings of alterations in both DLPFC and DIPPC function in schizophrenia during WM are consistent with the research, reviewed in more detail in another contribution to this series, suggesting a disconnection between frontal and parietal regions among individuals with schizophrenia (Kim et al., 2003; Meyer et al., 2001; Schlosser et al., 2003a,b). Importantly, the regions of PPC showing altered functional connectivity with frontal cortex among individuals with schizophrenia were in the DIPC area thought to be important for central executive function. Such findings of course raise the question of how DIPPC contributes to central executive function. A number of suggestions have been put for the role of DIPPC in executive processing. One intriguing hypothesis is that the DIPC makes a specific contribution to the temporal coding of items within working memory using magnitude codes (Marshuetz et al., 2000) in coordination with the dorsolateral prefrontal cortex (D'Esposito et al., 1999b). In schizophrenia, this coordinated activity of the DIPC and DLPFC may be disturbed during WM, leading to difficulties coding the temporal order of items within a working memory task (Brahmbatt et al., 2004).

Relationship to normative models of working memory function

In summary, the literature on WM in schizophrenia provides clear evidence for behavioral impairments on tasks measuring central executive and manipulation functions, but less clear evidence for impairments on tasks measuring maintenance functions of WM, such as the phonological loop or the visual–spatial scratchpad. Further, the literature on WM-related brain activation in schizophrenia provides consistent evidence for altered activity in DLPFC and DIPPC (or connectivity between the two), but much less evidence for impaired activity in regions thought to support domain specific buffer systems (VLPFC and VIPPC). Thus, the literature on WM function in schizophrenia could be taken as providing evidence for a dissociation between deficits in manipulation versus maintenance components of WM, providing evidence for the validity of making this distinction in normal WM function.

Despite the fact that the data in schizophrenia can be seen as consistent with models of WM such as those put forth by Baddeley, the pattern of results in individuals with schizophrenia could be seen as somewhat inconsistent with the models of WM developed in the animal literature. Specifically, the seminal work by Goldman-Rakic (1987) on the neural basis of WM in non-human primates suggested that neurons in DLPFC showed sustained delay-related activity during performance of WM tasks, even when the delays were not filled with any distracting information. The types of tasks used in these animal studies are ones that would tend to be considered "maintenance only" type tasks in the human literature. However, as described early, the human literature does not necessarily suggest a large role for DLPFC in the "simple" maintenance of information in WM, especially not of single items as in many of the non-human primate studies. Further, research on individuals with lesions to DLPFC does not suggest that these individuals are impaired on simple forward span tasks, thought to measure the maintenance of information in WM (D'Esposito and Postle, 1999). The literature on schizophrenia could be viewed as consistent with the DLPFC lesion literature, with relatively little impairment on span forward tasks, but evidence for impairment on central executive and manipulation tasks as well as altered DLPFC function. Thus, there is somewhat of a discrepancy between the non-human primate literature, which suggests a role for DLPFC in the maintenance of information over unfilled delays, and the human literature, which does not necessarily suggest a critical role for DLPFC in WM maintenance.

This discrepancy might be addressed by looking at delayed-match-to sample tasks in humans, as these are tasks that be more analogous to the non-human primate tasks than are the span forward tasks. D'Esposito and Postle (1999) have suggest that delayed-match to sample tasks are more likely to require rehearsal mechanisms than span tasks, given that span tasks allow one to immediately repeat back the items. In contrast, delayed-match to sample tasks often have relatively longer delays which may necessitate some type of rehearsal or refresh mechanisms to keep the information active, particularly if there is distracting information introduced during the delay. In a review of WM performance in individuals with lesions to DLPFC, D'Esposito and Postle (1999) found evidence for impaired delayed-match-to-sample performance among individuals with DLPFC lesions. However, these impairments were most evident for tasks that included filled delays and thus necessitated protection from interference.

This later finding is actually consistently with non-human primate data suggesting that delay-related activity in DLPFC is particularly important for WM performance in monkey when distracting repeating items intervene between the cue and the probe (Miller et al., 1995).

In the schizophrenia literature, there is also clear evidence for impaired behavioral performance on delayed-match-to-sample tasks, though many of these studies have used tasks that involved some type of distraction during the delay (Goldberg et al., 1998; Lencz et al., 2003; Park and Holzman, 1992), potentially turning the paradigm into a dual task or protection from interference task (which some might suggest engages the central executive). There have been a few studies using delayed-match-to-sample tasks without any distraction that have shown impairments among individuals with schizophrenia (Tek et al., 2002), though some of studies have either not included a no-delay condition (to establish it as a maintenance deficits) (Coleman et al., 2002), or have used more than one or two items in the memory set (leading to the possibility for a role for chunking, a potential type of manipulation) (Goldberg, 1984; Kim et al., 2004). Thus, analogous to individuals with DLPFC lesion, there is evidence for impaired delayed-match to sample performance among individuals with schizophrenia, with the greatest evidence for impairment in conditions that include distracting information.

The fact that the DLPFC lesion and schizophrenia literatures point to some evidence for impairments in the maintenance of information in WM, particularly during distraction, is consistent with the suggestion from the non-human primate literature that the DLPFC is important for maintenance as well as manipulation components of WM. However, the healthy human literature does still suggest a much larger role for DLPFC in manipulation as compared with maintenance, and few studies demonstrate strong DLPFC activation when only an item or two has to be maintained in WM. Further, the Baddeley model of WM does suggest a relatively strict segregation between maintenance and central executive components of WM, a view which is not necessarily consistent with a role for the same regions of DLPFC in both maintenance and WM (though engagement of different regions of DLPFC for maintenance versus manipulation would of course be quite consistent with Baddeley's model). As such, it is not clear how to resolve these seemingly contradictory views of the relationship between DLPFC function, and the maintenance versus manipulation components of WM.

DLPFC and context processing

A way in which my colleagues and I have to tried to resolve this seemingly contradictory views of the functional roles of DLPFC in WM is to postulate that one way in which DLPFC contributes to central executive function is to maintain certain types of information—context representations—that helps to guide the processing and manipulation of other information. More specifically, Cohen and colleagues (Barch et al., 2001; Braver et al., 1999; Braver and Cohen, 1999; Cohen et al., 1999; Cohen and Servan-Schreiber, 1992) have used computational modeling techniques to help put forth the hypothesis that intact function of dopamine in DLPFC is responsible for the processing of context, and that a disturbance in this mechanism is responsible for a range of cognitive deficits in schizophrenia. Context refers to prior task-relevant information that is represented in such a form that it can bias selection of the appropriate behavioral response. Context representations can include task instructions, a specific prior stimulus, or the result of processing a sequence of prior stimuli (e.g. the interpretation that results from processing a sequence of words in a sentence). Because context representations are maintained in an active state, they are continually accessible and available to influence processing. Consequently, context can be viewed as the subset of representations within WM that governs how other representations are used. One important insight that has emerged from this work is a single deficit in one aspect of executive control can contribute to deficits in cognitive domains often treated as independent. As such, we have argued that deficits in WM, attention and inhibition in schizophrenia can all be understood in terms of a deficit in context-processing (Barch et al., 2001; Braver et al., 1999; Braver and Cohen, 1999; Cohen et al., 1999; Cohen and Servan-Schreiber, 1992). When a task involves competing, task-irrelevant processes (as in the Stroop task), we have argued that context representations serve to inhibit such task-irrelevant processes by providing top-down support for task-relevant processes. When a task involves a delay between a cue and a later contingent response, we have argued that the mechanism used to represent context information is used to maintain task relevant information against the interfering, and cumulative effects of noise over time (as in a delayed-match-to-sample paradigm). Further, in both inhibition and WM conditions, context representations serve an attentional function, by selecting task-relevant information for processing over other potentially competing sources of information.

Thus, the context hypothesis can explain why patients with schizophrenia demonstrate deficits on at least some tasks thought to tap WM, as well as deficits on other cognitive control tasks that may not involve a high WM load (e.g. Stroop) (e.g. Barch et al., 1999). Further, the context-processing hypothesis explains why patients show deficits on tasks in which context information needs to be determined and maintained, even if this context information constitutes a low WM load (Barch et al., 2003; Cohen et al., 1999). The context hypothesis may also help to explain why individuals with schizophrenia (and those with lesions to DLPFC) do particularly poorly on delayed-match-to-sample tasks that include distraction, as context information may play a critical role in tagging the to-be-protected information or in signifying the need for either rehearsal refreshes or the inhibition of the distracting information.

Several studies have provided support for the hypothesis that individuals with schizophrenia have deficits in context-processing. Behavioral studies have found selective patterns of performance deficits among patients with schizophrenia on tasks specifically designed to measure context-processing (Barch et al., 1998, 2001, 2003; Cohen

et al., 1992, 1999; Condray et al., 1999; Javitt et al., 2000; Niznikiewicz et al., 1997; Servan-Schreiber et al., 1996; Stratta et al., 1998, 2000; Titone et al., 2000). In addition, the siblings of individuals with schizophrenia who do not themselves have schizophrenia also demonstrate a selective deficit in context-processing (MacDonald et al., 2003) as do individuals with schizotypal personality disorder (Barch et al., 2004), suggesting that such deficits may indeed be associated with liability to schizophrenia. In terms of DLPFC activity, medication naïve first episode patients with schizophrenia demonstrate impaired DLPFC activation associated with impaired context-processing (Barch et al., 2001), while psychotic individuals with disorders other than schizophrenia do not show the same impairment in DLFPC activity (MacDonald et al., 2005). Chronic-medicated patients with schizophrenia also show impaired DLPFC activity associated with impaired context-processing (MacDonald and Carter, 2003; Perlstein et al., 2003).

Of course, the verbal description of context processing provided above does not necessarily make clear how this helps to explain a role for DLPFC in the maintenance of information over filled or unfilled delays, as in delayed-match-to-sample tasks. However, work using computational simulations that specify the role of dopamine in DLPFC in relationship to WM and executive control deficits in schizophrenia can help to provide a more mechanistic understanding of the role of DLPFC in WM (Braver et al., 2002). For example, a number of studies suggest that various indices of altered DLPFC integrity (task-related functional brain activation, NAA, WM performance) are associated with evidence for hyperdopaminergic function in subcortical systems (Abi-Dargham et al., 2002; Bertolino et al., 1999; Meyer-Lindenberg et al., 2002). Such findings are consistent with recent modifications of the context processing theory of cognitive dysfunction in schizophrenia, which suggests that phasic dopamine bursts generated by subcortical systems normally serve to regulate the gating of information, including context representations, into WM (Braver and Cohen, 1999, 2000; Braver et al., 2002). Abnormalities in the activity of the subcortical dopamine system then dysregulate the ability to appropriately gate information into WM, leading to both perseverative behaviors when WM representations cannot be updated, and susceptibility to interference due to poor stability of WM representations. Thus, intact dopamine inputs into DLPFC may be critical for guiding what information should be gated into WM buffers and maintained over delays, as well as for helping to gate out potentially distracting information that could interfere during a delay period. Findings that modulation of the DA system can improve WM and or executive function performance in schizophrenia (Barch et al., 1997b; Daniel et al., 1989, 1991) or in individuals with poor WM function (Mattay et al., 2003) are at least indirectly consistent with the tenets of the context processing theory.

The arguments put forth above suggest that the representation and maintenance of context is a function that is different from the maintenance of identity information, and potentially different from other aspects of manipulation. As noted above, the functional imaging literature provides some evidence for the distinction between the maintenance of identity and the maintenance of context information, in that the maintenance of context reliably engages DLPFC (Barch et al., 1997a, 2001; Braver and Bongiolatti, 2002), while the maintenance of identity information does not always engage DLPFC (D'Esposito et al., 1999b). Further, individuals with schizophrenia often show an intact ability to maintain one or two identity items in working memory, but are impaired on the maintenance of a single "context" representation on the AX-CPT task (Cohen et al., 1999). However, the dissociation of context processing from other types of manipulation has not yet examined empirically. For example, it would be interested to compare the regions of DLPFC engaged by context processing versus other forms of manipulation within the same individuals, as well as to examine whether manipulations of the dopamine systems have similar or different influences on context processing versus manipulation within the same individuals (either healthy individuals or those with schizophrenia).

CONCLUSION

In summary, the literature on WM function in schizophrenia does support the important of distinguishing between the maintenance and manipulation components of WM. Individuals with schizophrenia show relatively little evidence of impairment on tasks thought to be primarily reliant on the phonological loop, a key component of the verbal maintenance system. Further, individuals with schizophrenia tend to show relatively intact activation in brain regions thought to be important for the mechanisms involved in the phonological loop, such as VLPFC (articulatory rehearsal) and VIPPC (phonological coding or storage). It is less clear whether individuals with schizophrenia show deficits in visual–spatial scratchpad function, primarily because there are not yet clear behavioral markers of the function of this system. Individuals with schizophrenia show clear evidence of deficits on tasks thought to measure various aspects of central executive function and manipulations, as well as robust evidence for impairments in brain regions thought to be associated with executive function, such as DLPFC and DIPPC. However, there is some discrepancy been the models of WM developed in the human and non-human primate literature, particularly in regards to the role that DLPFC plays in the maintenance versus central executive component of WM. The non-human primate literature suggests more of a role for the DLPFC in maintenance components of WM, while the human literature has implicated the DLPFC more in executive processing. The literature on schizophrenia is mostly easily seen as consistent with the view that DLPFC is most involved with various aspects of executive processing, though individuals with schizophrenia do show some evidence of impairment on delayed-match-to-sample maintenance tasks, though most robustly on versions that include distracting information during the delays. To resolve these discrepan-

cies, we have suggested that the DLPFC can be involved in the maintenance of information, but of a specific type (context representation) that helps to guide and coordinate other information held in WM. Further, we have suggested that dopamine deficits in DLPFC among individuals with schizophrenia contribute to deficits in context processing.

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